DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

TRANSMITTED BY FACSIMILE

Nancie A. Zecco, Senior Regulatory Associate
Alkermes, Inc.
88 Sidney Street
Cambridge, MA 02139

RE: NDA 021897
Vivitrol® (naltrexone for extended-release injectable suspension)
MACMIS #18584

Dear Ms. Zecco:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed the Patient Welcome Kit (VIV 700) which includes a consumer DVD entitled, "Real Stories of Recovery" (testimonials) (VIV 703B) and Touchpoints Insert Card (patient brochure) (VIV 704 for Vivitrol® (naltrexone for extended-release injectable suspension) (Vivitrol) submitted by Alkermes, Inc. (Alkermes) under cover of Form FDA-2253. The testimonials and patient brochure are false or misleading because they minimize important risk information associated with the use of Vivitrol and overstate the efficacy of the drug. The patient brochure also fails to adequately communicate the drug's indication. Thus, the promotional materials misbrand the drug in violation of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 352(a) & 321(n). *Cf*. 21 CFR 202.1(e)(3)(i); (e)(5)(i), (iii); (e)(6)(i) & (e)(7)(viii). Furthermore, the Patient Welcome Kit or any of the enclosed pieces do not appear to have been disseminated with the full FDA-approved product labeling (PI) for Vivitrol, in violation of 21 CFR 201.100(d).

Background

The INDICATIONS AND USAGE section of the FDA-approved product labeling (PI)[1] for Vivitrol states the following (in pertinent part):

> VIVITROL is indicated for the treatment of alcohol dependence in patients who are able to abstain from alcohol in an outpatient setting prior to initiation of treatment with VIVITROL.
>
> Patients should not be actively drinking at the time of initial VIVITROL administration.
>
> Treatment with VIVITROL should be part of a comprehensive management program that includes psychosocial support.

The DOSAGE AND ADMINISTRATION section of the PI states the following (in pertinent part):

[1] The PI submitted with the above-mentioned promotional pieces and the version referred to within this letter is dated October 2007. However, the most recent version of the approved PI is dated October 2010.

> The recommended dose of VIVITROL is 380 mg delivered intramuscularly every 4 weeks or once a month.

Vivitrol is also associated with a number of serious risks, including the following Boxed Warning concerning hepatoxicity:

Hepatoxicity

> Naltrexone has the capacity to cause hepatocellular injury when given in excessive doses.
>
> Naltrexone is contraindicated in acute hepatitis or liver failure, and its use in patients with active liver disease must be carefully considered in light of its hepatotoxic effects.
>
> The margin of separation between the apparently safe dose of naltrexone and the dose causing hepatic injury appears to be only five-fold or less. VIVITROL does not appear to be a hepatotoxin at the recommended doses.
>
> Patients should be warned of the risk of hepatic injury and advised to seek medical attention if they experience symptoms of acute hepatitis. Use of VIVITROL should be discontinued in the event of symptoms and/or sign of acute hepatitis.

Vivitrol is contraindicated in patients receiving opioid analgesics, patients with current physiologic opioid dependence, patients in acute opiate withdrawal, any individual who has failed the naloxone challenge test or has a positive urine screen test for opioids. Vivitrol is also contraindicated in patients who have previously exhibited hypersensitivity to naltrexone, PLG, carboxymethylcellulose, or any other components of the diluent of the injection. The PI includes Warnings related to eosinophilic pneumonia, unintended precipitation of opioid withdrawal, and opioid overdose following an attempt to overcome opiate blockade. The PI also contains a number of Precautions, including depression and suicidality, injection site reactions, renal impairment, use in patients with thrombocytopenia or any coagulation disorder, and use in patients who are pregnant, plan to become pregnant, or are breastfeeding. Furthermore, the most common side effects associated with the use of Vivitrol include injection site reactions, nausea, tiredness, headache, dizziness, vomiting, decreased appetite, painful joints, and muscle cramps.

Additionally, the CLINICAL STUDIES section of the PI states the following (in pertinent part):

> The efficacy of VIVITROL in the treatment of alcohol dependence was evaluated in a 24-week, placebo-controlled, multi-center, double-blind, randomized trial of alcohol dependent (DSM-IV criteria) outpatients. Subjects were treated with an injection every 4 weeks of VIVITROL 190 mg, VIVITROL 380 mg, or placebo.

Minimization of Risk Information

Promotional materials are misleading if they fail to present information about risks associated with a drug with a prominence and readability reasonably comparable with the presentation of

information relating to the effectiveness of the drug. Promotional materials must also include risk information in each specific part as necessary to qualify any safety or effectiveness claims made in that part.

While the testimonial videos prominently present efficacy claims about Vivitrol during the testimonial portions, they fail to convey **any** risks for Vivitrol during these portions of the videos. Risk information is presented after the testimonials towards the end of the videos, where it is unlikely to draw the viewer's attention. Additionally, this information is presented with music playing in the background, using a telescript format with rapidly scrolling text in small type font and no accompanying audio presentation, thus making it very difficult to read and process this important risk information.

Furthermore, while the 24-page patient brochure presents numerous efficacy claims on the first 19 pages, it fails to include **any** risk information for Vivitrol until page 20. Thus, the only risk disclosure for Vivitrol is relegated towards the end of the brochure. We note that the statement, "PLEASE SEE ENCLOSED IMPORTANT PATIENT INFORMATION" is included in small type font at the bottom of several pages of the brochure; however this does not mitigate this misleading impression.

In addition, the testimonial for the patient "Jason S." describes him as "[a] 30-year-old patient with alcohol dependence and a history of liver problems." This description minimizes the risk of hepatotoxicity included in the Boxed Warning section of the PI because it fails to include the important material information that "Naltrexone is contraindicated in acute hepatitis or liver failure, and **its use in patients with active liver disease must be carefully considered in light of its hepatotoxic effects**" (emphasis added)." While we acknowledge that the Boxed Warning pertains to patients with "active" liver disease and not a "history" of liver disease as described in this testimonial, we are concerned that this distinction will not be clear to the majority of consumers viewing this video; therefore, the overall effect of omitting this important material information undermines the communication of and minimizes the serious risk of hepatoxicity associated with Vivitrol.

The overall effect of the risk presentations in the testimonial videos and brochure minimizes the serious risks associated with Vivitrol and misleadingly suggests that Vivitrol is safer than has been demonstrated by substantial evidence or substantial clinical experience.

Overstatement of Efficacy

Promotional materials are misleading if they suggest that the drug is better or more effective than has been demonstrated by substantial evidence or substantial clinical experience.

The testimonial videos contain an introduction that begins with a voiceover and superimposed text that states, "Alcohol dependence is a chronic illness and causes serious problems with relationships, health, work, and finances." This introduction is followed by a screen that directs the viewer to various patient testimonials. The testimonials include statements such as the following:

- Chris H: "Rehab wasn't going to do it. . . . It [Vivitrol] sounded like something that I wanted to try. I noticed that . . . My time with my son has always been really

important, but I'm really much more present, I'm much more positive. I'm a much better dad. . . . My son is thrilled. . . . I feel like someone familiar, but who has been away for a long time and that's a nice feeling for me – and a positive one. "

- Jason S: "Once it [my drinking] started to become an every day occurrence and she [my girlfriend] started to see the way that I would act, with me being selfish or me being ill-tempered, or whatever you know would set me off at the littlest snap of the fingers. . . . Vivitrol supplemental therapy changing the way you live your life. . . . It really did help my relationships to go on Vivitrol."

- Tina S: "The money was going towards alcohol and not the kids. I couldn't go to their functions at school or their baseball games 'cause I was always too buzzed. Couldn't drive, you know. As they grew they really lost a lot of respect for me. With the drinking, DSS got involved. . . . Julie at the clinic, she suggested Vivitrol. . . . Since I've been on the shot. . . . I feel better about myself now that I'm sober. I've got a little bit more respect from the kids and that I feel like a mother now. Physically I'm in better shape than I was. . . . Couldn't even crawl out of bed and now I'm back to work. . . . My life has changed so much in the past year. I've gotten remarried. We're working on the house and everything's going pretty good."

- Chris J: "I've had six [DUIs] . . . and I was incarcerated for the DUIs. . . . When I was in jail . . . he [my dad] had told me about a drug called Vivitrol. . . . Thanks to my sobriety, I've been able to enjoy my job better. I've recently started school again. I actually show up this time. I have a really wonderful relationship with my family. I was invited to my family reunion for the first time in four or five years this past year. My girlfriend . . . we've been together over seven months now. So it's just been one after another after another of these great things that have happened to me. Vivitrol helps you get on the right path. "

Similarly, the patient brochure includes the following statements (emphasis in original):

- "'***I wanted to prove something to my son—that I could be the father that he's going to need*** . . .'
— Chris H, age 38, former musician, currently attending nursing school" (page 3)

- "'***I feel better about myself. I've got more respect from my kids. I feel like a mother and I'm back to work***.'
—Tina S, age 40" (page 7)

- "'**I was invited to this year's family reunion for the first time in 5 years, and I had fun**.'
—Chris J, age 26, restaurant worker" (page 19)

The patient brochure also includes the following statements (emphasis in original; footnote omitted):

- "**Ten reasons for quitting**
    1. **You will feel better physically.**

2. **You will have a better relationship with your family.**
3. **You will have a better relationship with your friends.**
4. **You will have fewer problems at your job.**
5. **You will have more money to spend on other things.**
6. **You will feel more active and alert.**
7. **You will accomplish more of the things you want to get done.**
8. **You will feel better about yourself.**
9. **You will regain your self respect.**
10. **You will experience personal and spiritual growth.**" (page 5)

- "**You can do it**
  Remind yourself of what you hope to achieve
  - Self-respect
  - Emotional balance
  - Spiritual growth
  - Financial security
  - Respect of family
  - Respect of friends
  - Physical health
  - A better job
  - Peace of mind
  - Serenity
  - A happy heart
  - Freedom from alcohol
  - Children's love
  - Another chance at life" (page 18)

These claims misleadingly overstate the efficacy of Vivitrol by implying that the usual outcome of treatment with Vivitrol is a positive effect on a patient's interpersonal relationships, emotional functioning, work productivity, productivity in general, and overall quality of life. FDA is not aware of substantial evidence or substantial clinical experience to support such effects of Vivitrol treatment. Claims of such treatment benefits must be supported by substantial evidence or substantial clinical experience as demonstrated through adequate and well-controlled trial(s) using well-developed instruments that reliably and validly measure the specific concepts at issue. If you have data to support such claims, please submit them to FDA for review.

The "Chris H." testimonial video includes the following claim regarding his experience after being treated with Vivitrol:

- "I was starting to sleep, starting to get to sleep."

The above claim misleadingly overstates the efficacy of Vivitrol by implying that the drug has a treatment benefit for improving sleep onset. Claims regarding sleep-related outcomes require positive findings using objective tests of sleep such as polysomnography. We are not aware of substantial evidence or substantial clinical experience to support this effect of Vivitrol. If you have data to support this claim, please submit them to FDA for review.

Moreover, we note that the ADVERSE REACTIONS section of the PI lists insomnia/sleep disorder as a common adverse event in ≥5% of patients treated with Vivitrol.

The testimonial videos also include claims such as the following (emphasis added):

- Jason S: "Received VIVITROL therapy for 12 months"
- Tina S: "Received VIVITROL therapy for 18 months"
- Chris J: "Received VIVITROL therapy for 12 months"

In addition, the patient brochure includes the following claim (bolded emphasis in original; underlined emphasis added):

- "'***I'm going to counseling and I'm on my tenth shot of VIVITROL*** . . ..' *– Jason S, age 30, financial advisor*" (page 13) (Note: Recommended dose is every 4 weeks or once a month)

The above claims misleadingly overstate the efficacy of Vivitrol by implying that Vivitrol has demonstrated efficacy up to 10, 12, or 18 months. However, according to the CLINICAL STUDIES section of the Vivitrol PI, "The efficacy of VIVITROL in the treatment of alcohol dependence was evaluated in a 24-week, placebo-controlled, multi-center, double-blind, randomized trial of alcohol dependent (DSM-IV criteria) outpatients" (emphasis added). Thus, Vivitrol has only been evaluated for efficacy for a period of about **six months**. FDA is not aware of substantial evidence or substantial clinical experience demonstrating the effectiveness of Vivitrol beyond 24 weeks. We acknowledge that the ADVERSE REACTIONS section of the PI contains information regarding patients treated with Vivitrol for six months or more and one year or longer; however this does not constitute substantial evidence or substantial clinical experience to support claims of efficacy beyond six months. If you have data to support such claims, please submit them to FDA for review.

Inadequate Communication of Indication

The patient brochure presents several efficacy claims for Vivitrol, but fails to adequately communicate its full indication. We note that the brochure includes the following statements:

- "Your doctor has prescribed VIVITROL to target the biologic urge to drink. To be effective, treatment with VIVITROL must be used along with other alcohol recovery measures, such as psychosocial counseling, mutual support, and faith-based groups." (page 10)

However, this does not adequately communicate Vivitrol's full indication. This information about Vivitrol's indication is not presented until page 10 of the 24-page brochure. Additionally it fails to communicate the important limitations to the indication that, "VIVITROL is indicated for the treatment of alcohol dependence in patients who are able to abstain from alcohol in an outpatient setting prior to initiation of treatment with VIVITROL. Patients should not be actively drinking at the time of initial VIVITROL administration" (emphasis added).

Failure to Provide Adequate Directions for Use

The Patient Welcome Kit or any of the enclosed pieces do not appear to have been disseminated with the full FDA-approved product labeling (PI) for Vivitrol, in violation of 21 CFR 201.100(d).

Conclusion and Requested Action

For the reasons discussed above, the patient testimonial videos and brochure misbrand Vivitrol in violation of the Act, 21 U.S.C 352(a) & 321(n). *Cf*. 21 CFR 202.1(e)(3)(i); (e)(5)(i), (iii); (e)(6)(i) & (e)(7)(viii). Furthermore, the Patient Welcome Kit or any of the enclosed pieces do not appear to have been disseminated with the full FDA-approved product labeling (PI) for Vivitrol, in violation of 21 CFR 201.100(d).

DDMAC requests that Alkermes immediately cease the dissemination of violative promotional materials for Vivitrol such as those described above. Please submit a written response to this letter on or before November 19, 2010, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Vivitrol that contain violations such as those described above, and explaining your plan for discontinuing use of such violative materials. Please direct your response to me at the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD 20705-1266, or facsimile at 301-847-8444. In all future correspondence regarding this matter, please refer to MACMIS# 18584 in addition to the NDA number. We remind you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Vivitrol comply with each applicable requirement of the Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Susannah K. Hubert, MPH
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SUSANNAH HUBERT
11/04/2010